EMIL VON BEHRING

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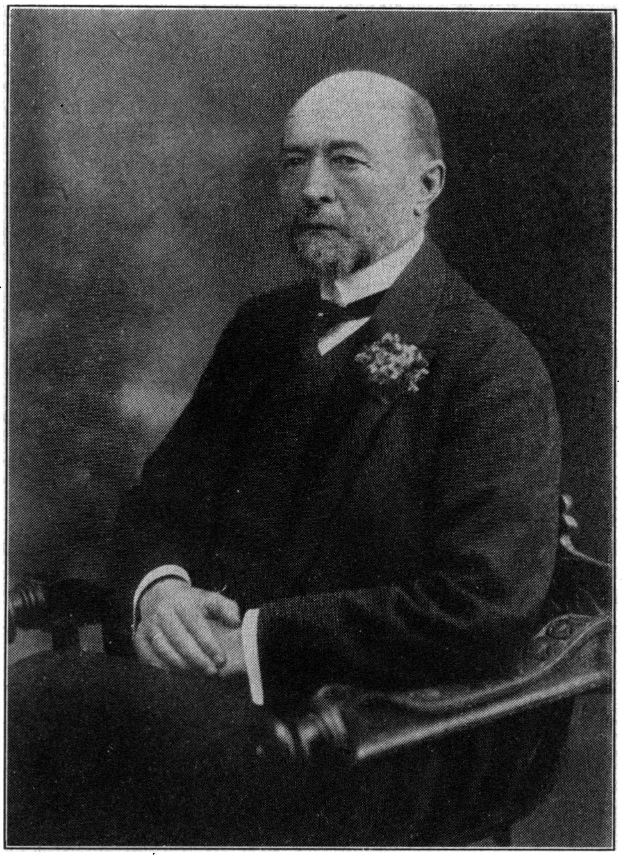
BY

Sir ARTHUR S. MacNALTY, K.C.B., M.D., F.R.C.P. F.R.C.S.

Formerly Chief Medical Officer of the Ministry of Health

The Army Surgeon

Emil von Behring, "one of the greatest benefactors of humanity" (*British Medical Journal,* 1929), was the son of a schoolmaster, who had 11 other children. He was born at Hansdorf, Deutsch-Eylau, West Prussia, on March 15, 1854, the day following the birth of Paul Ehrlich. He took his doctor's degree at the University of Berlin in 1878 and passed the State examination in 1880. He began his career as a military surgeon, serving in the Army Medical Corps, first at Posen, then in 1887 at Bonn, as staff surgeon, and lastly in the same rank in 1888 at the Army Medical College, Berlin. His first published paper (1887) dealt with iodoform as an antiseptic.



Emil von Behring.

While still an army surgeon Behring was impressed by the discoveries in bacteriology which were revealing the cause of a number of diseases, and especially by the great work of his compatriot Robert Koch. In the early 'eighties, therefore, he began a series of investigations which were the precursor of his main life-work. Bacteriologists had noted already that white rats were immune to anthrax, while wild rats were susceptible. Behring took the fresh serum of white rats and tested it on anthrax bacilli *in vitro*. In a short time the bacilli were killed. Nuttall had made similar observations on the bactericidal powers of the fresh sera of man and of several animals, and his observations, together with Behring's findings, led to the humoral theory of defence against the invasion of germs into the animal body.

Discovery of Diphtheria Antitoxin

By 1889 Behring had left the army and had become an assistant to Koch at the Institute of Infectious Diseases, Berlin, then a stimulating and productive centre of bacteriological research. In 1884 F. Loeffler had been deeply immersed in the study of diphtheria and had issued his exhaustive work on the bacillus of the disease, which he identified with the bacillus described by Klebs in the preceding year. Kitasato had discovered the bacillus of tetanus. Both diphtheria and tetanus were shown to be diseases caused by the local multiplication of the organism without penetration into the body generally. The hypothesis was then advanced that these two bacilli secreted soluble poisons which, being absorbed, acted on the cells of the central nervous system and other organs of the body.

Loeffler's work had been subsequently confirmed by many observers, but particularly by Roux and Yersin at the Pasteur Institute in a series of three important memoirs (1888–90). They also announced that they had grown diphtheria bacilli in broth and removed the bacilli by filtration through unglazed porcelain; the resulting sterile filtrate on injection into animals produced the characteristic symptoms of diphtheria; this soluble poison they termed a toxin.

These important results aroused universal interest. Loeffler had also been engaged in searching for the hypothetical toxin, and in 1890 Brieger and C. Fraenkel prepared a toxic substance from cultures of the diphtheria bacillus in bouillon, which they called "toxalbumin." By injections of this toxalbumin into guinea-pigs, Fraenkel established an immunity, so that 14 days later the animals were resistant to a virulent living culture of *C. diphtheriae.* These results were published in the *Berliner klinische Wochenschrift* on December 3, 1890, and on the following day, December 4, there appeared in the *Deutsche medicinische Wochenschrift* Behring and Kitasato's classical paper, entitled "Ueber das Zustandekommen der Diphtherie-Immunität und der Tetanus-Immunität bei Thieren." One week later (December 11) Behring, alone, published another paper, in the same journal, dealing with immunity against diphtheria and enumerating five different methods by which this could be obtained.

These papers announced the great discovery that an animal immunized against tetanus and diphtheria by graduated injections of killed broth cultures of these bacilli produces in its blood substances which are capable of neutralizing the toxic action of these bacilli. It was also shown that an animal previously injected with the serum of such an immunized animal was resistant to an otherwise fatal dose of bacilli or toxin; and, in addition, that an animal when treated with the serum, even if symptoms developed, could be cured. The substance in the serum of immunized animals was given the name of "antitoxin" by Behring and Kitasato. As the treatise on diphtheria of the Medical Research Council (1923) states: "In these papers we have the details of one of the greatest discoveries ever made in medicine. . . . History must assign unchallenged to E. Behring the merit of the discovery of antitoxin. It came at the end of a long period of research in which the bactericidal action of the blood had been very thoroughly studied."

These experimental results opened the gate of the new field of serum therapy for mankind. In quick succession many papers appeared confirming and amplifying Behring's discovery, including further papers by Behring himself and by Ehrlich.

Treatment of Diphtheria in Man

The practical application of the discovery to the treatment of diphtheria in man was advanced by the further work of Behring and Baer and of Behring and Wernicke. The antitoxic serum was tested in children with favourable results. The first child treated by antitoxin was a patient in von Bergmann's clinic in Berlin, the injection being made by Geissler on Christmas night, 1891. The firm of Meister, Lucius, and Bruning began to immunize animals in their factory at Hoechst in 1892.

In 1893 Behring had the title of professor conferred upon him. In this year with Kossel and Heubner he recorded the first cases in man treated with the new remedy.

Émile Roux, with his fellow-workers Louis Martin and Yersin, was mainly responsible for bringing diphtheria immunization from the experimental to the practical stage. Roux and Martin were the first to immunize horses, and were thus enabled to produce antitoxic serum in large quantity. In the hospitals of Paris serum treatment of diphtheria was established by 1894. In that year Roux was able to announce in his famous address at the International Congress of Hygiene and Demography at Budapest that the case mortality in children suffering from diphtheria in the Paris children's hospital had already been reduced from 52 to 25%.

In England in the summer of 1894 E. W. Goodall first treated by the new method some 20 patients suffering from diphtheria with favourable results, in the Eastern Hospital, Homerton; he used serum supplied to him by Sir Joseph Lister, who had obtained it from Roux. Goodall stated in his book (*A Short History of the Epidemic Infectious Diseases,* London, 1934) that in the autumn of the same year Armand Ruffer prepared antitoxin at the British Institute of Preventive Medicine, now the Lister Institute, and this serum was first used at the Eastern Hospital on October 23, 1894. It has lately been put on record that Sir Charles Sherrington used the first antidiphtheritic serum made in this country on October 15, 1894. The serum was prepared by Ruffer and himself at the Brown Institution. The patient, a boy of 8 years, was regarded as dying from diphtheria. He recovered. (See *Marginalia* contributed by Sir Charles Sherrington to *Science, Medicine, and History: Essays on the Evolution of Scientific Thought and Medical Practice written in honour of Charles Singer.* Oxford University Press, 1953, Vol. II, 550.).

Ehrlich's Standardization

In 1895 a control station was set up in Berlin for testing antitoxin; in 1896 this became an institute for serum research and testing, first at Steglitz (Berlin), and from October 1, 1899, at Frankfurt under the direction of Paul Ehrlich. He produced a quantitative method for determining the antitoxic value of any sample in units defined in relation to a stable standard of reference; his method is still the most accurate of all such biological titrations, and, incidentally, he laid down the main principles for all standardizations by the use of biological tests, which subsequently provided a basis for the accurate dosage of many different types of new remedies (Dale, 1950). By Ehrlich's work a good antitoxin with a precise measurement of its activity was made available to mankind, and antitoxin could be given in an adequate dose at the onset of diphtheria. The mortality of the disease, in such cases, fell to insignificant proportions. Ehrlich therefore greatly extended the practical application of Behring's discovery to the cure of diphtheria in man.

International Recognition

Within a few years the administration of antitoxic serum to patients suffering from diphtheria became a routine method of treatment. In an address, "The Aims and Achievements of Serum Therapy," delivered at the Naturalists' Congress in 1895, Behring said: "I have no fear that the thought which forms the basis of serum therapy will ever disappear out of medicine!" He estimated that antitoxin treatment produced a reduction of 75% in the mortality from diphtheria in Germany, an annual credit of 45,000 human lives. For this work Behring shared with Roux the 25,000 francs prize of the Paris Academy of Medicine and the 50,000 francs prize of the Institute of France. In 1901, when he received with Roux the Nobel Prize for medicine, he delivered an address at Stockholm on serum therapy. Orders and distinctions in the years following 1895 were showered upon him by learned societies of all European countries. Nor was the prophet without honour in his own country. In 1895 he received the title of Medical Privy Councillor and in 1901 a patent of nobility.

Researches on Tuberculosis

In 1894 Behring became Professor at Halle, and in 1895 was appointed to the Chair of Hygiene at the University of Marburg and Director of the Institute of Hygiene. Ill-health compelled him to give up systematic lecturing and teaching, and he gave only an occasional public lecture. After 1901 he turned his attention to the problem of immunization in tuberculosis. His premises were that human and bovine tuberculosis were but varieties due to the same organism; that infection in man and animals takes place in early life in the alimentary canal and pulmonary tuberculosis is a sequel to such intestinal infection; and that few human or bovine subjects escape infection before reaching adult life. The first two premises were not generally accepted. He attempted to immunize calves against tuberculosis with an attenuated strain of human tubercle bacilli, but the results were disappointing. His bovo-vaccine was largely used in Germany, Russia, Sweden, and America, and for a time aroused much interest. It has not withstood the test of time and prolonged experiments.

For the treatment of human beings von Behring prepared a form of tuberculin, named "tulase," by the action of chloral on tubercle bacilli. The exact method of preparation of tulase was unfortunately kept secret. It was eventually found not to be superior to any other form of tuberculin. He also did experiments on human immunization with killed tubercle bacilli.

As already mentioned, von Behring believed at first that human and bovine tubercle bacilli were identical, and, though there was a time when he favoured their dual nature, he returned in the end to his original belief. He also considered that tuberculosis was a lifelong affection; and contemporaries often quoted his aphorism that "phthisis is but the end of a lullaby sung at the cradle of the prospective consumptive." His experimental work in tuberculosis, although disappointing, was an introduction to the problem of immunization against tuberculosis in man and bovines.

Von Behring was financially interested in the manufacture of antitoxic sera by the great commercial firm of Farbwerke Höchst, which built and equipped laboratories on a well-planned and extensive scale for him. Here he conducted researches in which were used 7,000,000 oz. of cultures of tubercle bacilli. He was also interested in another commercial enterprise, the Behringwerke, which manufactured his bovine-vaccine. As a consequence of these interests von Behring rose to affluence and became the owner of a large estate on which grazed herds of cattle, which he also used for experimental purposes.

In 1905 he had investigated the collection of milk by aseptic methods and its preservation by formalin and hydrogen peroxide. He was the author of numerous articles on the experimental therapeutics of anthrax and streptococcal infections, the hygiene of the milk supply, water, and other subjects. He also wrote books on blood serum therapy (1892), the aetiological treatment of infectious diseases (1893), the history of diphtheria (1893), and the general treatment of infectious diseases (1898).

Discovery of Toxin–Antitoxin

In the study of diphtheria von Behring had achieved fame, and in 1913 he introduced his new preparation for protection against the disease. With Wernicke he had shown in 1892 that immunity to diphtheria was produced by a protective dose of antitoxin. Later work by Goodman, Lohr, and others showed that such immunity does not persist after two to three weeks from the inoculation. It appears that Behring and Wernicke discovered in 1898 that immunity against diphtheria could be produced by doses of diphtheria toxin neutralized by antitoxin in experimental animals, but it was not until 1913 that von Behring gave his " new " preparation to the world. Theobald Smith in 1907, as the result of successful experiments upon guinea-pigs, had suggested that a toxin-antitoxin mixture might be used for preventive inoculation in man, but it was left to von Behring to achieve this. The preparation of his nearly neutral mixture of diphtheria toxin and antitoxin was varied from time to time, and gradually rendered less toxic.

Active Immunization in Diphtheria

Von Behring's toxin-antitoxin mixture was the forerunner of modern prophylaxis in diphtheria, and here again he must be acclaimed as a pioneer in immunization. The practical application on a large scale in New York City was due to the work of W. H. Park and to Bela Schick's skin test with a small dose of diphtheria toxin, which gave evidence of the need of the individual for immunization and of its success when applied. Sheldon Dudley's work and tests on young naval personnel assisted in establishing the value of the method in Great Britain. The immunizing reagent (toxin-antitoxin) has been modified in various ways—for example, the production of toxoid by treating the toxin with formaldehyde (toxoid-antitoxin mixture), etc. In Hamilton, Ontario, the incidence and mortality from diphtheria had shown little change for years up to 1925, when general immunization began. Thereafter, both fell so rapidly that there has been no death from diphtheria since 1930 and no case of the disease since 1933. Similar excellent results have been secured in other parts of Canada and in the United States of America. In this country successive Chief Medical Officers of the Ministry of Health have advocated artificial immunization since 1922, but, in spite of official memoranda and the co-operation of a number of medical officers of health, both incidence and mortality of diphtheria continued high. The incidence varied between 69,480 cases in 1920 to 46,281 in 1940 (England and Wales). At the end of 1940 the Ministry of Health undertook the free provision of prophylactics, the cost of which had been borne by local rates. This provision undoubtedly aided the campaign for immunization, which during the war years and subsequently has been vigorously pressed. In 1952 only 376 cases of diphtheria and 32 deaths in England and Wales were recorded, as compared with 23,199 cases and 934 deaths in 1944.

Such are the encouraging sequelae of von Behring's pioneer work in diphtheria immunization.

Von Behring in his later years was subject to severe periods of mental depression, which the advent of the first world war exacerbated. He died at Marburg of an acute attack of pneumonia on March 31, 1917.

The Significance of von Behring's Work

In the course of this paper reference has already been made to the significance of von Behring's work. In general terms it can be said that he was one of the founders of immunology as a science, and that Ehrlich's standardization of diphtheria antitoxin augmented its potentialities. Tetanus antitoxin, the discovery of von Behring and Kitasato, was another striking example of passive immunization, and its value has been proved in the prophylactic treatment of the disease. The specific sera which neutralized the other sporing anaerobic bacteria causing gas gangrene, together with tetanus antitoxin, helped to reduce these deadly complications of soil-contaminated wounds in two world wars. Antisera have also been used in dysentery due to the Shiga bacillus, and in the treatment of pneumococcal pneumonia and cerebrospinal meningitis. The use of all these antibacterial sera has largely given place to chemotherapy. In 1935 came the sulphonamides and later penicillin, streptomycin, and other antibiotics. It is of interest here to note that von Behring at first attempted to produce a disinfection in the body by a great variety of chemical substances. With trichloride of iodine he partially succeeded in curing some cases of experimentally produced diphtheria in animals, and his comparison of their blood with normal blood may have aided him in the discovery of antitoxin.

It is a far better thing to prevent disease than to cure it. Active immunization against disease began with Jenner and was applied by Pasteur. Koch and von Behring were unsuccessful in tuberculosis, but Wright's typhoid vaccine has helped to abolish typhoid fever as a scourge of armies. The B.C.G. vaccine of Calmette and Guérin, involving the administration of a living culture of the tubercle bacillus rendered avirulent, has now become the subject of experimental trial in this country. The assessment of the real value of antibacterial vaccines is very difficult. Von Behring's initiation of toxin-antitoxin immunization and its later triumphs have already been described in this paper. Immunization with tetanus toxoid is a more modern instance of successful prophylaxis. Immunization against virus infections, of which the most successful is that against yellow fever, is another recent advance, and work is proceeding on vaccines designed to overcome the viruses of influenza and of poliomyelitis. Much of this successful work in the conquest of disease during the present century has followed from von Behring's pioneer researches, and his discovery of diphtheria antitoxin and toxin-antitoxin. Remembering the great boon he conferred upon mankind by these discoveries and the way he opened to the prevention of this killing disease of childhood, it is fitting, therefore, that the centenary of his birth should be honoured in Great Britain.

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The spread of certain diseases from one country, and even from one continent, to another is facilitated by air travel. Insects such as mosquitoes, flies, fleas, and lice may carry diseases dangerous to man. Perhaps most serious are malaria, yellow fever, virus encephalitis, sleeping sickness, typhus, and plague. According to Dr. P. H. Bonnel, of the epidemiological services of World Health Organization, the behaviour of insects in aircraft in flight has been the subject of close scientific observation. Such observations have shown that altitude and changes in air pressure and temperature during long flights do not permanently affect the activities of the insects. The vibrations in modern aircraft are reduced to a minimum, and insects which penetrate into a plane can live there for as long as they can exist without nourishment—that is, if they cannot find what they need in the aircraft itself. It was noted that certain insects laid their eggs on the outside of aircraft, on the wings, the fuselage, the rudder, and even on the propellers. These eggs were found to be still there at the end of the journey: neither the wind nor the altitude nor yet changes in temperature had affected their capacity for survival. On one single plane thousands of larvae emerged from the eggs and swarmed over the surface of the aircraft. Strict surveillance of aircraft and of aerodromes is therefore absolutely essential. This passive defence can be effective, however, only if it is complemented by more active measures which remove all possibility of transporting live insects in aircraft. Active control measures consist in spraying aircraft with insecticidal aerosols containing pyrethrin or D.D.T., but countries vary in their methods and in when " disinsectization " is performed. The application to the interior of aircraft of certain new resinous varnishes in which are incorporated residual insecticides is perhaps the best and simplest means of control. This important aspect of international prevention of disease is one of the subjects dealt with by the W.H.O. committee on international quarantine.